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HEAD AND NECK CANCER WITH MICROVASCULAR RECONSTRUCTION

Prospective, randomized, blinded clinical study on effects of dexamethasone on postoperative recovery, long-term quality of life, and mortality

Satu Kainulainen

University of Helsinki
Faculty of Medicine
Doctoral Program in Clinical Research

Department of Oral and Maxillofacial Surgery
Helsinki University Hospital

HEAD AND NECK CANCER WITH MICROVASCULAR RECONSTRUCTION

PROSPECTIVE, RANDOMIZED, BLINDED CLINICAL STUDY ON EFFECTS OF DEXAMETHASONE ON POSTOPERATIVE RECOVERY, LONG-TERM QUALITY OF LIFE, AND MORTALITY

Satu Kainulainen

ACADEMIC DISSERTATION

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SUPERVISED BY
Docent Patrik Lassus
Head of the department
Department of Plastic Surgery
Helsinki University Hospital
University of Helsinki
Helsinki, Finland

Docent Anna-Maria Koivusalo
Administration
Helsinki University Hospital Area
University of Helsinki
Helsinki, Finland

REVIEWED BY
Docent Esko Veräjänkorva
Department of Plastic Surgery
Turku University Hospital
University of Turku
Turku, Finland

and

Docent Heikki Irjala
Department of Otorhinolaryngology – Head and Neck Surgery
Turku University Hospital
University of Turku
Turku, Finland

OPPONENT
Docent Andres Rodriguez-Lorenzo
Department of Plastic and Maxillofacial Surgery
Uppsala University Hospital
Uppsala, Sweden

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications:

I. Kainulainen S, Törnwall J, Koivusalo AM, Suominen AL, Lassus P. Dexamethasone in head and neck cancer patients with microvascular reconstruction: No benefit, more complications. *Oral Oncol*. 2017 Feb;65:45–50. doi**:** 10.1016/j.oraloncology.2016.12.008.

II. Kainulainen S, Lassus P, Suominen AL, Wilkman T, Törnwall J, Thorén H, Koivusalo AM**.** More harm than benefit of perioperative dexamethasone on recovery following reconstructive head and neck cancer surgery: a prospective double-blind randomized trial. *J Oral Maxillofac Surg*. 2018 Nov;76(11):2425–2432. doi: 10.1016/j.joms.2018.05.007

III. Kainulainen S, Koivusalo AM, Roine RP, Wilkman T, Sintonen H, Törnwall J, Thorén H, Lassus P. Long-term quality of life after surgery of head and neck cancer with microvascular reconstruction: a prospective study with 4,9 years follow-up. *Oral Maxillofac Surg* (2019). https://doi.org/10.1007/s10006-019-00806-w.

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ABBREVIATIONS

ALT	Anterolateral thigh flap
ASA	American Society of Anesthesiologists
BMI	Body mass index
CCI	Charlson Comorbidity Index
CRP	C-reactive protein
DCIA	Deep circumflex iliac artery
DEX	Group of patients receiving dexamethasone
DSS	Disease specific survival
ERAS	Enhanced Recovery After Surgery
FFS	Free flap surgery
GC	Glucocorticoid
HME	Heat and Moisture Exchanger
HNC	Head and neck cancer
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
HR	Hazard ratio
HRQoL	Health related quality of life
ICU	Intensive care unit
IMRT	Intensity-modulated radiotherapy
IV	Intravenous
LD	Latissimus dorsi
MSCT	Multislice computerised tomography
NON-DEX	Control group
OPSCC	Oropharyngeal squamous cell carcinoma
OR	Odds ratio
OS	Overall survival
PEG	Percutaneous endoscopic gastrotomy
PET	Positron emission tomography
PONV	Postoperative nausea and vomiting
QoL	Quality of life
RFA	Radial forearm
RRs	Risk ratios
RT	Radiation therapy
SCC	Squamous cell carcinoma
SK	Satu Kainulainen (co-author of articles I-IV)
TAPAS	Temporal artery based posterior auricular skin flap
US	Ultrasound
TNM	Tumor, node and metastasis
VAS	Visual analog scale

ABSTRACT

BACKGROUND

Surgery is usually the primary treatment of Head and neck cancer (HNC). It causes significant morbidity and large surgical defects that usually require microvascular reconstruction to restore the tissue deficiency. Treatments of these very challenging areas are associated with psychological disruption of life. Unfortunately, the studies of long-term Health-related quality of life (HRQoL) after microvascular reconstruction surgery of HNC are scarce. Complications related to microvascular surgery are quite rare, but they can be devastating. Prolonged treatment periods often exacerbate complications and therefore delay adjuvant oncologic treatments. Glucocorticoids (GCs) are widely used perioperatively to diminish immediate postoperative complications such as PONV, pain and swelling, but the evidence of their safety is unclear. Complex surgery of HNC and postoperative complications may influence survival and patients high long-term mortality is common.

AIM

This thesis is focused on three main aims: first, to evaluate whether the perioperative use of dexamethasone in reconstructive HNC surgery is beneficial (Study I-II); second, to evaluate the long-term HRQoL compared with an age- and gender-standardized sample of the general population (Study III); and third, to investigate whether the use of perioperative dexamethasone affects short-term mortality in HNC patients and to analyze the predictors affecting long-term mortality (Study IV).

PATIENTS AND METHODS

This study consisted of a prospective, double-blind randomized group of 93 HNC patients with a microvascular reconstruction operated at the Department of Oral and Maxillofacial Surgery and Department of Plastic Surgery in Helsinki University Hospital in Finland between December 2008 and February 2013. Patients were randomized into two groups, 51 patients received dexamethasone (DEX) and 42 served as a control group (NON-DEX). Patients in the study group received 10 mg dexamethasone intravenously (IV) every 8 h on the first day, every 12 h on the second day and once on the third day, total amount of dexamethasone being 60

mg. In studies I, II, and IV, the data was analyzed depending on randomization, in Study III, the data was analyzed for all patients independent of randomization.

RESULTS

Patients who received dexamethasone had significantly more major complications, especially surgical infections (p=0.012), and need for second surgery within three weeks. Dexamethasone use failed to diminish the amount of neck swelling, length of stay in the intensive care unit (ICU) or hospital, or duration of intubation or tracheostomy (Study I).

The use of dexamethasone did not reduce postoperative nausea and vomiting (PONV) in five days (p>0.05). Patients in the DEX-group received less oxycodone in five days postoperatively (p=0.040) and reported significantly less pain (p=0.030). Patients required significantly more insulin and lactate levels were higher (p<0.001) (Study II).

The long-term (4.9-years) HRQoL of operated HNC patients was significantly lower than at baseline (p=0.010). The most affected dimensions were "speech" and "usual activities" at the end of follow-up. The HRQoL was a significantly lower in HNC patients as compared with the general population (p=0.014)(Study III).

Perioperative use of dexamethasone was associated with higher short-term mortality in reconstructive HNC surgery. During the first year, more deaths occurred in the DEX group than in the NON-DEX group: at one month 4% vs 0%, at six months 14% vs 0% and at 12 months 22% vs 5% (p=0.043). HNC was the primary cause of death in most of the deceased (79%). The most important long-term predictors of death were distant metastases (p<0.001), CCI 5-9 (p<0.001), and the use of perioperative dexamethasone (p=0.004)(Study IV).

CONCLUSIONS

The results of this thesis conclude that the perioperative use of dexamethasone is not recommended for reconstructive HNC patients requiring microvascular reconstruction. It is associated with major complications and higher short-term morbidity, and it does not seem to significantly enhance immediate post-operative recovery or shorten ICU or hospital stay. Long-term HRQoL was significantly reduced and speech and usual activities were the most affected dimensions up to 4.9-years after the operation in the whole patient cohort. There is more harm than benefit of the perioperative use of dexamethasone with reconstructive HNC patients.

1. INTRODUCTION

Head and neck cancer (HNC) is the sixth most common malignancy in the world and its incidence is increasing worldwide. In Finland, over 800 patients are diagnosed annually, constituting 2.5% of all new malignant diagnoses (1, 2). HNC includes malignant neoplasms of the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, salivary glands, upper esophagus, paranasal sinuses, nasal cavity, and skin. The treatment options vary from surgery to oncological treatments, or combinations of these. The primary treatment of HNC is often surgical resection of the tumor and affected lymph nodes in the neck area. Anatomically demanding surgery often causes large surgical defects that require free flaps to restore the tissue deficiency. In comparison to regional flaps, microvascular reconstruction is a more complicated surgery, but extremely reliable in achieving successful reconstruction in HNC (3).

Treatments of HNC, including surgery and possible oncological treatments, are associated with enormous psychological disruption of life by causing physical, aesthetic, and functional disability. HRQoL has become an important outcome in HNC treatment and there are many different disease-specific and generic HRQoL questionnaires to measure it (4, 5). The studies of long-term HRQoL after microvascular reconstruction surgery of HNC are scarce.

HNC surgery can cause many postoperative disadvantages, like respiratory problems caused by neck swelling, prolonged ICU and hospital stay, pain and PONV. GCs are widely used perioperatively to improve patient's recovery problems although the safety of their use with this patient group has not been studied earlier with prospective, randomized studies (6-8).

Complex surgery of HNC and postoperative complications may influence survival and high long-term mortality is common. Even if the disease-specific survival (DSS) has improved from 55% to 66% over the last decades, five-year overall survival (OS) has been reported to be around 50–60% (9-12). According to the literature, the presence of lymph node metastasis, invasion, tumor recurrence, postoperative complications, and advanced age have been described to be associated with worsened survival, but the results are controversial (10, 13, 14). The number of studies focusing on mortality after reconstructive surgery of HNC is limited. Early postoperative deaths are rare, but they occur in all major surgeries, thus it is important to analyze the mortality and associated factors also with reconstructive HNC patients.

2. REVIEW OF THE LITERATURE

2.1 HEAD AND NECK CANCER

Head and neck cancer is the sixth most common cancer worldwide and it includes cancers of the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, salivary glands, upper esophagus, paranasal sinuses, nasal cavity, and skin (15, 16). HNC comprises 2.5% of all new malignant diagnoses in Finland: with a population of 5.5 million people, over 800 new cases are reported annually, the majority occurring in men (1, 2, 17). The most common cancer is squamous cell carcinoma (SCC), which accounts for 90% of the head and neck malignancies. Other malignant neoplasms include sarcomas, lymphoma, malignant melanomas, metastases of other malignancies, and various carcinomas of the salivary glands.

2.1.1 ETIOLOGY, INCIDENCE, AND SURVIVAL

Smoking and alcohol consumption are both main independent risk factors that have been associated with the incidence of HNC. The interaction between tobacco and alcohol has been explored in several studies. In a pooled analysis of 18 case-control studies, Hashibe et al. reported that in users of tobacco and alcohol in Latin America, the overall risk of HNC was 10 times higher compared with never-users (18). The risk of developing HNC increases with the intensity and duration of smoking (19). Garrote et al. reported effective findings in their case-control study of 200 patients in Cuba where heavy alcohol users (> 21 drinks per week) and heavy smokers (>30 cigarettes per day) had a 111-fold risk of HNC than non-consumers. In the same study former drinkers who continued heavy smoking had still a 33.6-fold risk (20).

More recently the role of human papillomavirus (HPV) infection has been increasingly recognized and HPV-related tumors (HPV-16) represent a different biological, epidemiological and clinical subset of HNC that are represented more frequently with younger patients (aged < 60 years). The study of Mehanna et al. showed that 55% of 654 oropharyngeal SCC cases were HPV-16 positive (21). HPV-positive HNC:s (particularly oropharyngeal tumors) appear to have a more favorable OS rate compared with HPV-negative diseases (22).

The incidence of HNC is increasing in Finland (1, 17). Complex surgery for HNC may influence survival and high long-term mortality is common as five-year survival has been reported to be around 50% (10, 23-25). Typically, a patient's prognosis is based on tumor, node, and metastasis (TNM) classification. Staging

is an important tool for surgeons and oncologists to define a proper treatment and predict prognosis for each cancer. Periodic updates to staging systems are necessary and the latest update became effective in 2018, when oral cavity cancers began to also be staged by the depth of invasion. This novel staging system was introduced for HPV-associated oropharyngeal cancers and extra nodal extension began being used on all sites, except for nasopharyngeal and high-risk HPV oropharyngeal cancers (26, 27). HNC usually sends metastasis to lymph nodes and the most prognostic factor is the lymph node status. About 40% of oral cavity and pharynx SCC present with regional metastasis (28).

2.1.2 TREATMENT OF HNC

The treatment of HNC depends on a number of factors, including the location and the stage of the cancer and patient's general health. Treatment for HNC usually includes surgery, radiation therapy, chemotherapy, or a combination of treatments.

Surgery remains the primary treatment modality, especially for oral cancer. The primary surgical resection of the tumor with free margins and the dissection of the locoregional lymph nodes (neck dissection) is the most important goal of surgery without delaying possible adjuvant oncological treatment. Surgical margins are considered to be free when the specimen includes a five mm wide resection evaluated by a pathologist, and close when including a zero to five mm resection. Positive and close margins have negative impact on survival and recurrence (29, 30). The degree of the tumor and possible metastasis are evaluated preoperatively using Multislice computerized tomography (MSCT), Magnetic resonance imaging (MRI), ultrasound (US), or Positron emission tomography (PET) imaging. The treatment for early-stage SCC tumors (T1–T2) is usually single modality with surgery, while locally advanced larger (T3–T4) tumors are treated with surgery followed by adjuvant oncological treatment or with only definite oncological treatment (chemoradiation) (31, 32). In Finland, the most common radiation technique is intensity-modulated radiotherapy (IMRT), which can be combined with chemotherapy—usually Cisplatin. Adjuvant radiation dose after primary surgery is approximately 60–66 Gy to the primary site and node positive neck.

Treatment of oropharyngeal SCC (OPSCC) has changed toward a more oncologic approach during the last decades. The main reason for this is human papillomavirus (HPV) (33). Radiotherapy and oncological modalities are used as a primary treatment, especially on the tonsils or base of tongue area with human papillomavirus 16 positive (HPV16) patients and for inoperable patients (34). The HPV-associated form of OPSCC has been considered to have different cancer biology and has been shown to have better treatment response and survival than HPV-negative OPSCC (35). Relatively new oncological treatment methods include

modern immunotherapy with immunomodulating antibodies, which is designed to boost the body's natural defenses to fight the cancer with recurrent and/or metastatic HNC (36).

2.1.3 MICROVASCULAR RECONSTRUCTIONS OF HNC

The surgical closure of the defect includes direct closure of the wound, healing by secondary intention, skin or mucosal grafting, local flaps, pedicled flaps, and more complex free microvascular tissue transfer. In this study all patient cases included only surgery with microvascular reconstructions. Curative treatment of the HNC usually includes ablative surgery and microvascular reconstruction should be considered whenever reconstruction for surgical defects is needed and cancer is still operable (37–39). In extensive ablative cases, when the resection of facial nerve causes severe functional and esthetic disadvantages, the primary facial nerve reconstruction should also be considered to improve patients Quality of life (QoL) (40). Free flap surgery (FFS) have been in routine use in HNC for 20–30 years and was first introduced in HNC more than 50 years ago (41, 42). FFS is used as a standard reconstruction method when local or regional flaps are inadequate, when the result would cause significant loss of normal form and function, or when it could lead to a deterioration in the HRQoL (9, 43–45). FFS is technically demanding, each case is unique, and indications and contraindications should be carefully evaluated for each patient to achieve optimal results and minimize complications. Even if free flaps are extremely reliable in achieving successful reconstruction in skilled hands, complications and flap losses do occur which usually leads to a secondary FFS and can be devastating (46). Patients age is not a contraindication for FFS, as methods have been safe among the elderly as well (47).

2.1.4 FLAPS

There are numerous possibilities for free flap donor sites in HNC and the selection of the flap depends on the localization of the cancer, type of needed tissue, anatomical considerations, patient characteristics, and surgeons experience. More than 20 donor sites for FFS in HNC have been introduced during the last 30 years (42, 48). Free flaps can contain different tissue needed for reconstruction (skin, subcutis, muscle, bone) and they are usually classified according to their constituents as fasciocutaneous flaps (skin, fat, and fascia), muscle flaps (muscle), osseous flaps (bone), and combinations of these (osteocutaneous, myocutaneous, osteomusculocutaneous).

2.1.4.1 Soft tissue flaps

Radial forearm flap (RFA) has been widely used in HNC since the 1980s as described by Muhlbauer in 1982 (49, 50). The skin flap is harvested with superficial fat, the radial artery, concomitant veins and cephalic vein. It is extremely reliable, and anastomoses are usually easy to perform because vessels are large in diameter and the pedicle is long. Its advantages are a long vascular pedicle, and its thin, versatile soft tissue. The limitations of the flap include its relatively small size and visible donor-site.

Anterolateral thigh flap (ALT) as first published by Song et al. 1984 (51) and popularized by Koshima et al. in 1989 (52) is based on septocutaneous and musculocutaneous perforators of the descending branch of the lateral circumflex femoral artery and can be lifted as a subcutaneous, fasciocutaneous, or myocutaneous flap. It is reliable, harvesting is straight-forward, and there is a minimal donor-site morbidity (53).

Latissimus dorsi (LD) free flap as first described in HNC reconstruction in 1978 by Quillen et al. (54) is widely used in HNC surgery. It has a long pedicle (thoracodorsal vessels), which is unlikely to become affected by atherosclerosis and it offers a good stock of soft tissue. Other options for soft tissue flaps used in HNC surgery include several variations of the rectus muscle (55), ulnar artery flap (56), the median sural artery perforator flap (57), and temporal artery posterior auricular skin (TAPAS) flap (58).

2.1.4.2 Composite flaps

In complex HNC surgery with bony defect, vascularized bone grafts offer a better tool to achieve both structural stability and soft tissue support for anatomical and functional end results compared with soft-tissue flaps. The osseocutaneous fibular free flap is probably the most popular option used in composite HNC reconstruction because of its many advantages. It was first introduced for mandibular reconstruction in 1991 by Germain et al. (59). It has low donor-site morbidity, harvesting with two team approach simultaneously is relatively easy and the flap provides a good length of vascularized bone. Limited size of soft-tissue is its primary disadvantage. The deep circumflex iliac artery (DCIA) flap presented in 1979 by Taylor et al. (60) is widely used in HNC surgery and offers a thick, bulky bone with natural anatomic curvature for especially angular and corpus defects. The disadvantages include donor-site morbidity, a slightly more challenging elevation, and a limited length of pedicle. The scapular bone flap (61) is a very versatile flap with alternative soft tissue components and is widely used in HNC. The flap is well-suited for large defects and the donor-site morbidity is low. The drawbacks

include relatively thin bone material for dental rehabilitation (62) and harvesting requires repositioning of the patient. Wilkman et al. compared the three most used composite flaps (a total of 163 patients, scapular, fibular, and iliac crest) in maxillofacial reconstructions in Helsinki University Hospital and found that the deep circumflex iliac artery flap was the least reliable alternative of these (63).

In Finland, microvascular reconstructions have been the first choice for reconstruction since the 1990s. New flap variations are being developed with the aim to customize the choice of flap individually for every patient to achieve the best possible result. In recent years, the range of flaps has expanded. A chimeric flap provides diverse tissue types from a single donor site. It is composed of more than one flap that each have an independent vascular supply but in turn are joined to a single pedicle and its advantage includes the independent mobility of skin, muscle, and bone (64). Many combinations can be created, and the proportion of chimeric flaps have increased (65, 66). Examples of chimeric flaps include, for example, serratus-latissimus-scapular component flap and anterolateral thigh chimeric flap types. Husso et al. retrospectively analyzed the trends of microvascular reconstructions in the head and neck area between 1995–2012 at the Department of Plastic Surgery, Helsinki University Hospital, Finland and found that the majority of free flaps were single fasciocutaneous flaps (Radial forearm (RFA) and ALT) but the flap types increased over time, with a total of 24 different flaps (48).

2.1.5 RISKS AND COMPLICATIONS IN FFS

Many factors may have influenced FFS outcomes. Complications are common after microvascular reconstruction of the HNC. Reported rates of the frequency ranges between 34–85% (69). Different variables are considered as risk factors for complications within this group of patients, including comorbidities, smoking, alcohol use, increased age, ASA (American Society of Anesthesiologists) class, long duration of anesthesia, tracheostomy, higher tumor stage, and site (3, 67, 68, 70, 71). There are several tools to classify comorbidities in surgery, including the Charlson Comorbidity Index (CCI) score, introduced by Charlson et al. as an index of general comorbidity predicting mortality (72).

Vascular complications may jeopardize the survival of the flap and different types of free flaps have been shown to have differences in their blood flow. Mucke et al. studied changes in perfusion of four different flaps in a prospective study of 196 patients and found that after the first postoperative day, the perfusion of septocutaneous flaps (RFA) was much better compared with muscular flaps (73). Free flaps tolerate ischemia from 4 to 12 hours, thus revision should be performed during this time frame to save the flap (74). Most vascular occlusions (80%) occur within one to four postoperative days (75). Although, the survival rate

of the free flap is generally considered good, 95–98% (76, 77), every flap failure is devastating to the patient. The failure of the flap may occur for multiple reasons, like harvest of the flap, pedicle compatibility, prolonged ischemia, and inadequate postoperative care (78). In a study of 451 HNC FFS patients by Mucke et al., the overall free flap failure rate was 4% and revealed significant risks of flap failure depending on prior attempts at microvascular transplants ($p<0.001$ and length of hospitalization ($p=0.007$) (79).

Complications can be detected if the flap is visible and the follow-up meticulous. Most surgeons use clinical monitoring techniques, as observation of the flap color and turgor and pinprick testing (80, 81). In the hypopharynx or oropharynx area, flap can be situated deep and be invisible. The follow-up of these flaps through visualization is extremely difficult or even impossible. Doppler ultrasound may also be unreliable to use close to carotid arteries. The Licox® tissue oxygen pressure monitoring system has also been used to follow postoperative circulation in free microvascular flaps (82). There are several monitoring devices to follow the vitality of the flap, however many of the methods are quite expensive and no particular technique is superior to others (83).

Different classifications for complications are used but there is no specific method for HNC. Complications can be categorized as surgical, such as donor site or recipient site, related to surgical ablation or microvascular reconstruction, and medical complications including patients' medical condition. Minor complications can be treated with medications or at the bedside, but major wound- or flap-related complications may cause serious harm to patients' overall recovery. In this study, surgical complications were classified according to the Clavien-Dindo classification published in 1992, which is the most-cited system used in the literature and has become more common also in HNC (84, 85). McMahon et al. studied postoperative complications after HNC free flap surgery using the Clavien-Dindo classification in a prospective of 192 patients and found that a total of 64% had complications, and around one third of them were serious (69). The Clavien-Dindo classification is presented in **Table 1**.

Table 1. Clavien-Dindo classification

Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical interventions. Allowed therapeutic drugs as antiemetics, diuretics, antipyretics, and electrolytes, and physiotherapy. Allows wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than those allowed for Grade I complications. Blood transfusions and total parenteral nutrition are also included
Grade IIIa	Requiring surgical, endoscopic, or radiological intervention Intervention not under general anesthesia
Grade IIIb	Requiring surgical, endoscopic, or radiological intervention Intervention under general anesthesia
Grade IV	Life-threatening complication requiring IC/ICU-management
IVa	Single organ dysfunction (including dialysis)
IVb	Multiorgan dysfunction
Grade V	Death of a patient

Patients undergoing major HNC operations often need tracheostomy to secure the airway during the immediate postoperative period (86). There are no evidence-based recommendations for the use of tracheostomy or the timing of decannulation because of the variability of these patients and procedures. The majority of the patients are admitted to the ICU postoperatively due to careful free flap monitoring and controlled weaning off the ventilator, though there is no evidence for the positive impact of routine postoperative care in the ICU (87, 88). Free flap monitoring after surgery should be performed at least hourly for the first 24 hours postoperatively (89) to detect possible vascular problems over time. Patients earlier irradiation or previously failed microvascular operation have been reported to predispose to possible flap failure (78). In a study of 408 patients of Brown et al, vascular occlusions later than two days after the primary operation led to flap loss more often than in days one and two (90). Long hospital periods and major postoperative problems are common related side effects due to major surgery. Prolonged hospitalization can cause postoperative problems like nosocomial infections, as well as increased health care costs and delays to possible adjuvant oncological treatments (91).

2.2. GLUCOCORTICOIDS

GCs are a group of steroid hormones, the name is composed from its role in regulation of glucose metabolism, synthesis of adrenal cortex and its steroidal structure. CCs are part of the feedback mechanism in the immune system. The natural GC cortisol is produced and released from the adrenal cortex and

controlled by the hypothalamic-pituitary-gland. GCs are involved in a wide variety of cardiovascular, metabolic, homeostatic and immunological actions. Synthetic GCs act like normal cortisol but have different potencies and biological half-lives.

2.2.1 SYNTHETIC GLUCOCORTICOIDS IN MEDICINE

Usually GCs are used in medicine to treat diseases caused by overactive immune system like allergies, asthma, inflammatory and autoimmune diseases, organ transplant rejection, and malignancies of the lymphoid system (92). Their immunosuppressive action is well known although their precise mechanism remains unclear (93, 94). Various synthetic GCs are available for several indications. Synthetic GCs are different regarding their pharmacodynamics and can consequently be chosen based on the desired effects (95) (**Table 2**). For short-term use (less than one week) GC dosages are usually higher than those used over the long-term, and the benefits and side-effects are also different.

Table 2. Pharmacology of glucocorticoids

	Equivalent dose (mg)	Relative mineralocorticoid activity	Duration of effect (h)	Anti-inflammatory potency	Half-time in plasma (min)
Short-acting					
Cortisone	25	1	8–12	1	60
Hydrocortisone	20	0.8	8–12	0.8	90
Intermediate-acting					
Prednisone	5	0.25	24–36	4	60
Prednisolone	5	0.25	24–36	4	200
Methylprednisolone	4	0	24–36	5	180
Triamcinolone	4	0	24–36	5	300
Long-acting					
Dexamethasone	0.75	0	36–54	25	200
Betamethasone	0.6	0	36–54	25	200

* short: 8–12 hours, intermediate: 12–36 hours, long: 36–54 hours

2.2.2 GLUCOCORTICOIDS IN HEAD AND NECK SURGERY

Exacerbation of inflammation following surgery has been shown to be associated with negative postoperative outcomes like pain (96), therefore the reduction of inflammation is a common target used by anesthesiologists to prevent postoperative

complications (97). Administration of GCs intravenously perioperatively is common after a wide variety of surgical procedures, including microvascular head and neck surgery. GCs are given to patients because they are believed to relieve postoperative pain, decrease swelling, prevent postoperative nausea and vomiting (PONV), and possible facilitate early discharge, although the evidence of benefit in postoperative use is contentious (6, 98-100). GC use became widespread in oral and maxillofacial surgery in the 1950s (101) and several studies have shown the benefits of GCs on recovery (6). Dexamethasone is one of the most common drugs administered by anesthesiologists and systemic dexamethasone has been shown to minimize postoperative nausea (PONV), pain, and post-extubation sore throat (7, 99, 102).

2.2.3 EFFECTS OF DEXAMETHASONE

2.2.3.1 Benefits

Nausea, vomiting, and retching complicate recovery from anesthesia frequently, occurring in more than 30% of patients (103). There are many studies on the benefits of dexamethasone and anesthesiologists favor its perioperative use widely to diminish PONV and pain (8, 98, 104-107). Episodes of PONV may cause many complications, like gastric aspiration, wound dehiscence, psychological distress, and delayed recovery (108). Particularly in reconstructive head and neck surgery, PONV may jeopardize the primary healing of the reconstructed area. GCs have been proven to reduce edema after different type of surgeries such as orthognathic surgery (109), ophthalmologic interventions (110), third-molar surgery (111), and neurosurgery (112). Dexamethasone has also been shown to improve the quality of postsurgical recovery after elective cardiac surgery (113).

2.2.3.2 Side-effects

GC use may lead to serious side-effects, even with short-term use (less than one week), and particularly with high doses. Studies have shown that the short-term use of GCs can cause increased risk for avascular osteonecrosis (114-116), GC induced psychosis (117-119), and increase of peptic ulcers and gastrointestinal bleeding (120). Dexamethasone slows down the inflammation process, which has various adverse effects on tissue healing and may disturb surgical wound healing and cause postoperative infections (121-123). Studies of the influence of perioperative dexamethasone on oncological surgery outcomes are scarce. Yu et al. reported the use of dexamethasone to be associated with decreased OS when investigating

the effect of perioperative administration of dexamethasone on 515 rectal cancer patients (124).

2.3 HEALTH RELATED QUALITY OF LIFE (HRQOL) WITH HNC

Anatomically demanding surgery causes significant morbidity, and this affects patients who experience significant impact on quality of life (125). HRQoL has become an important instrument to measure the outcome of patients, also with HNC. HRQoL after surgical or oncological treatment of HNC is well studied and there are many disease-specific and generic HRQoL questionnaires to measure the quality of life of cancer patients (4, 5, 126, 127). Previous studies have shown that advanced tumors, extensive surgical resection, free flap reconstruction and postoperative radiotherapy are associated with low HRQoL (128-130).

The studies focusing on HRQoL after FFS for HNC patients are scarce and results contrary. Most of the studies report mild or moderate deterioration of global QoL. According to these studies, the acceptable level of global QoL was defined as comparable to population-based values (131-133). Some studies report QoL improved after FFS . Limitations of these studies include often short-term follow-up and variability in HRQoL instruments.

2.3.1 METHODS TO ASSESS QOL IN HCN

There have been different instruments to measure patients QoL available since the 1990s. Psychological well-being is individual and may vary greatly despite equal clinical outcome and treatment. Instruments can be generic or specific questionnaires and content of self-administrated questionnaires is variable (127, 134, 135). EORTC QLQ-H&N35 is one of the most commonly used specific questionnaire to measure QoL among HNC patients (136). It includes seven symptom scales and eleven single issues. Other HNC-specific questionnaires are, for example, UW-QoL and FACT-HN. Swallowing-specific QoL instrument MDADI (M.D. Anderson Dysphagia Inventory) is widely used with HNC patients (126, 137). There is no consensus regarding which instrument is preferable, and disease-specific instruments alone may not provide the most appropriate answers for this extremely challenging group of patients.

The 15D questionnaire is designed in Finland for populations aged over 15 years. Use of 15D enables comparison of the HRQoL results with an age-standardized general population. It has been used in many cancer patient groups (138) including with HNC (139, 140). The 15D compares with other generic HRQoL instruments like the NHP, SF-20, SF-6D, and EQ-5D and a study by Richarson et al. ranked the

15D first among the most frequently used generic HRQoL instruments in sensitivity and construct validity in the area of cancer (141).

The 15 dimensions of the instruments are: moving, seeing, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, distress, depression, vitality, and sexual activity. The respondent chooses one of the five levels best describing his/her state of health at the time (the best level = 1; the worst level = 5) for each dimension. The 15D can be used as both a single index score measure and a profile measure. The single index number (15D score) ranges from 0 (dead) to 1 (full health) and the 15D score is calculated from the health state descriptive system (142). The change or difference of +/- 0.015 in the score is considered clinically important (143-146).

2.4 MORTALITY AFTER RECONSTRUCTIVE HNC SURGERY

The complex anatomy and functions of the HNC region often lead to the need for reconstructive surgery. Postoperative problems may influence survival and high mortality is common despite advances in treatment. With an ageing population, HNC patients undergoing surgery are often older and tend to have comorbidities which can affect slowing the healing process and postoperative outcome. The presence of lymph node metastasis, invasion, tumor recurrence, postoperative complications, and advanced age have been described to be associated with worsened survival in some previous studies, but the results are contradictory (10, 13, 14).

2.4.1 MORTALITY

The number of studies focusing on mortality after reconstructive surgery due to HNC is limited. Since FFS has been routinely used in HNC reconstruction globally, it is important to remember that something more serious than flap failure can happen postoperatively and to investigate what factors may associate with this. Even if the DSS has improved from 55% to 66% over the last decades (11, 12), five-year OS has been reported to be around 50–60% (9, 10). Previously published studies reveal that the five-year survival of HNC patients with microvascular reconstruction is lower (43–66%) than HNC patients in general (66%) (147, 148).

2.4.2 CAUSES OF DEATH

Causes of death of non-operated HNC survivors have been well described in both the short-term and long-term. Baxi et al., analyzed 35,958 non-metastatic head and neck squamous cell carcinoma (HNSCC) patients who survived at least 3 years from diagnosis and discovered that second primary malignancy (lung, esophagus, and colorectal cancer) was the leading cause of death, not the primary disease (149). Only a few earlier studies have focused on causes of death after FFS in HNC. Especially long-term results are limited. Tanaka et al. studied 1249 HNC patients treated with free flaps and found short-term (30-day) mortality to be 0.88% but long-term survival was not analyzed. The most common cause of death in one month was cerebral infarction (150).

3. AIMS OF THE STUDY

The aim of the present study was to investigate the prospectively collected group of patients with HNC and microvascular reconstruction.

The specific aims were as follows:

1. To examine whether the perioperative use of dexamethasone in reconstructive HNC surgery is beneficial for the patients.

2. To clarify whether the perioperative use of dexamethasone in HNC would improve the quality and speed of patients' recoveries and the effects on pain, PONV, lactate levels, and need for insulin after microvascular surgery.

3. To evaluate the long-term HRQoL of HNC patients with microvascular reconstruction compared to an age- and gender-standardized sample of the general population.

4. To investigate whether perioperative dexamethasone influences short-term mortality and to assess the causes of death and the predictors affecting long-term mortality in reconstructive HNC patients.

4. PATIENTS AND METHODS

This study consisted of a prospective, double-blind randomized group of 93 HNC patients who had a microvascular reconstruction and were operated at the Department of Oral and Maxillofacial Surgery and Department of Plastic Surgery in Helsinki University Hospital, Finland between December 2008 and February 2013.

In studies I, II, and IV the data was collected from randomized patients; in Study III, the data was collected from all patients independent of randomization.

4.1 ETHICAL CONSIDERATIONS

This study followed the Declaration of Helsinki for medical protocol and ethics and was approved by the regional Ethical Review Board of Helsinki University Central Hospital, Finland in 2008. The study was registered with EudraCT protocol (2008-000892-11). All patients signed a written informed consent form prior to randomization.

4.2 OUTCOME VARIABLES

The main outcome variables were as follows:

Study I: Major complications, neck swelling, length of ICU and hospital stay, duration of intubation or tracheostomy and possible delay to the start of radiotherapy if needed.

Study II: Speed of recovery (ability to sit, stand, walk, drink fluids), pain, PONV, glucose balance, metabolic and inflammatory response.

Study III: Health-related quality of life (long-term).

Study IV: Mortality (short-term and long-term), causes of death

4.3 PREDICTOR VARIABLES

The primary predictor variable was the perioperative use of dexamethasone (studies I, II, and IV). Other predictor variables included in the analyses were: start of

using Heat and Moisture Exchanger (HME), time of drainage removal time, start of communication, sitting, standing, walking, drinking fluids, transferring to the hospital ward and home, the change in patients weight during hospital stay, age, sex, smoking, use of alcohol, Body Mass Index (BMI), history of alcohol use (major, moderate, or none), length of surgery, the ASA, Charlson Comorbidity Index (CCI), major complication, length of sedation (as duration of propofol infusion), opioid infusion, amount of pain medications, insulin, antiemetics and IV antibiotics, lactate and C-reactive protein (CRP)/Leukocyte levels (studies I-II). Alcohol use was defined as moderate if drinking was weekly or less, and major if it occurred daily. In all studies, the tumor classification, tumor site, type of reconstruction, possible postoperative radio/chemotherapy, and number of postoperative surgeries were analyzed. In study IV the primary (intermediate) cause of death was used in the analyses and possible tumor recurrence or metastasis were collected from patient records.

4.4 PATIENTS

Patients with HNC who underwent microvascular reconstruction were operated and included in the study between December 2008 and February 2013 at the Department of Oral and Maxillofacial Surgery and the Department of Plastic Surgery, Helsinki University Hospital, Finland. All patients were evaluated by the multidisciplinary head and neck tumor board of the Helsinki University Hospital. Altogether 110 patients participated in the study, 55 in each group, and 10 were excluded. Exclusion criteria were peptic ulcer, history of liver or kidney dysfunction, glaucoma, psychosis from use of steroids, allergy to any constituent of the dexamethasone preparation used, and absence of written informed consent—97 patients met the criteria. Four of these patients were later excluded, one because he was administered additional dexamethasone and three because of intraoperative cancellation of free flap reconstruction. Therefore, 93 patients were included in the study: 73 from the Department of Maxillofacial Surgery and 20 from the Department of Plastic Surgery. Patients were randomized into two groups: 51 received dexamethasone (Oradexon®, DEX), and 42 were controls (NON-DEX) (**Figure 1**). Discrepancy in the size of the two groups is explained by the effect of luck of random selection. A total dose of 60 mg of dexamethasone was administered to patients in the DEX group intravenously over three days peri- and postoperatively (10 mg every 8 hours on the first day, every 12 hours on the second day, and one dose on the third day). The group information was provided in a sealed envelope to the anesthesiologist in charge of the anesthesia of the surgery and the anesthesiologist administered all doses to the patient, surgeons were unaware of which group the patients were assigned.

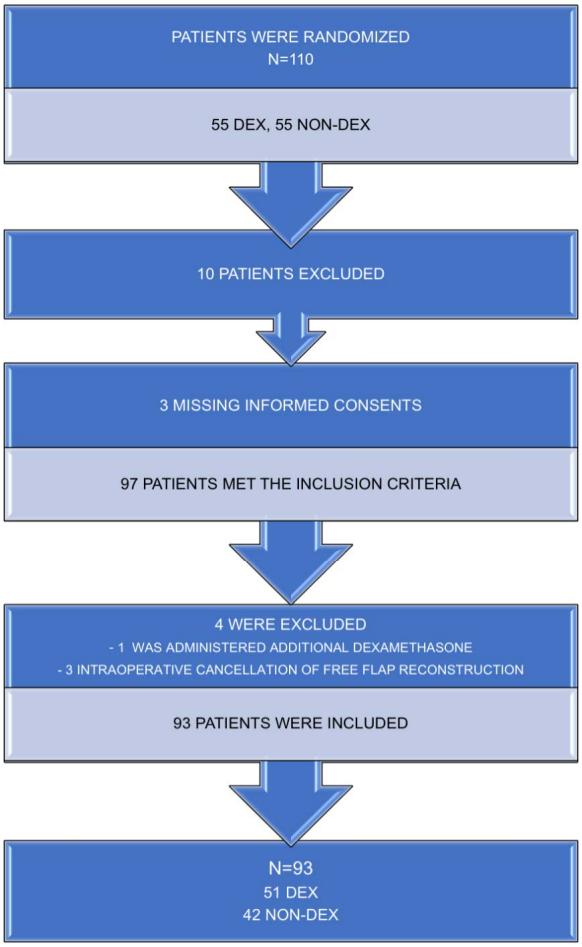

Figure 1. Patient selection (Study I, II, and IV)

4.4.1 PATIENTS POSTOPERATIVE CARE

Patients received standard, balanced anesthesia with continuous infusion of propofol and alfentanil. After the operation in the ICU, sedation was discontinued, and the patient was weaned from the respirator. The vitality of the microvascular flap was verified regularly. CRP, leukocyte count and lactate levels were measured for five days postoperatively. The targeted glucose level was 5–8 mmol/l and maintained with insulin infusion; insulin consumption and the total daily amount of insulin was registered. Free flaps were monitored with clinical examination, through visualization and checking the vital signs of the flap with pinprick tests every hour on the first postoperative day, and every two to four hours after that during the first three days.

4.4.2 MEDICATIONS AND FOLLOW-UP

Patients received antibiotics; cefuroxime 1.5 g x 3 IV and metronidazole 500 mg 1 x 3 IV over an average of 7 days, starting on induction of general anesthesia. Allergic patients received clindamycin 300 mg x 4 IV. Pain was measured using a 10-cm Visual Analog Scale (VAS) pain scores from 0 to 10 (0 indicating no pain and 10 indicating maximum pain). VAS was always measured before pain medication was administered. Patients were given paracetamol 1g x 3 IV, or oxycodone 0.2–0.4 mg/10kg IV, as a pain medication in the postoperative period if the patients scored more than 4 on a VAS, or when requested. No non-steroidal-anti-inflammatory analgesics were given. Nausea was treated with ondansetron 4 mg IV when needed. The data was collected and sorted from the follow up forms and hospital database by one physician (SK). Patients neck swelling was measured daily from the highest and marked point for 7 days postoperatively and the highest increase in the neck circumference (cm) in comparison to preoperative circumference was used for analysis. Patient rehabilitation (ability to sit, stand, walk, drink fluids) was recorded and patients were followed for 30 days after surgery for any surgical or medical complications. Surgical complications were classified according to Dindo *et al.* so that all the major complications were included to the complication group (IIIb) or worse and needed secondary surgery within three weeks (84, 85). Minor complications included local bed-side treatment and no need for further surgical interventions in the operation room.

4.4.3 HEALTH RELATED QUALITY OF LIFE (STUDY III)

HRQoL of the patients was measured with the multidimensional, generic 15D instrument (15D) **(Appendix)**. The 15D data for the general population came from the representative National Health 2011 Survey and for best comparison, those individuals were selected from the Helsinki University Hospital catchment area, and were in the same age range as the patients (n=1148). This sample reflected the age and gender distribution of the patients. All patients filled in the baseline 15D questionnaire before surgery and follow-up questionnaires were sent to all patients alive in a prepaid, pre-addressed envelope in October 2016. All patients who answered the follow-up questionnaire were included in the analysis and HRQoL was studied regardless of patient group. The influence of tumor site, use of microvascular reconstruction, tumor stage, and postoperative RT on long-term HRQoL were investigated.

4.4.4 MORTALITY (STUDY IV)

Causes of death for deceased patients were obtained from Statistics Finland and patients were followed up until the end of the year 2017. The primary cause of death (intermediate) was used in the analysis and causes of death were divided into three categories: HNC, non-HNC (other cancer than HNC), and other cause of death (cardiovascular, liver cirrhosis). Additional variables were collected from patient records including data of patients' free flap type, tumor location and stage, BMI, alcohol use, smoking, ASA, CCI, possible postoperative RT or chemotherapy, number of complications, number of surgeries, and possible tumor recurrence or metastasis. Factors associated with mortality were studied during the long-term follow-up.

4.5 STATISTICS

Descriptive statistics were reported as means and standard deviations (SD), medians or percentages. SPSS software was used for analyses in Studies I to IV and R 3.6.1 software was used for Study IV (R Core Team, 2019. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) (151). The significance of associations between groups and variables were evaluated by T-tests and Wilcoxon two-sample tests, Chi-square tests (Studies I–IV), or ANOVA were performed (Study III–IV). Risk ratios (RRs) with 95% confidence intervals were calculated to analyze the risk of outcomes in Studies I, II, and IV. Differences in mean values between groups and continuous variables were assessed by logistic regression and multivariate linear regression analysis was performed (Studies I, II, and IV). Kaplan-Meyer plot was used to compare the survival of the patients in the two study groups and variables for the multivariate model were selected using variables that were significant in the univariate model and/or have clinical relevance, and least absolute shrinkage and selection operator (Study IV) (152). Results from logistic regression analyses were reported as odds ratios (OR), and results from Cox's proportional hazard models as hazard ratios (HR). Power analysis to determine the number of patients needed was performed on the original material.

5. RESULTS

5.1 PERIOPERATIVE DEXAMETHASONE AND COMPLICATIONS IN HNC PATIENTS WITH MICROVASCULAR RECONSTRUCTION (STUDY I)

There were no major statistical differences between the groups regarding preoperative demographic data, except there were more major alcohol users in the NON-DEX group (DEX n = 8 (16%), NON-DEX n = 13 (31%), p=0.038 and more tracheostomized patients (60% vs 33%, p=0.034). Demographic statistics of the 93 patients and surgical data are shown in **Table 3 and Table 4**. Patients TNM classification is presented in **Table 5**.

There were significantly more major complications (need for second surgery in general anesthesia within three weeks), especially surgical infections (DEX 27% vs NON-DEX 7%), during the postoperative period in patients receiving dexamethasone (p=0.012) (**Table 6**).

Table 3. Demographic data of the patients (Study I–IV)*

Demographic characteristics and comorbidities	All (n=93)	DEX (n=51)	NON-DEX (n=42)	p
Age (years)	65 (34–93)	65 (39–93)	65 (34–88)	0.798
Male/Female	59/34	32/19	27/15	0.878
BMI	24.9 (15.8–42.7)	25.5 (15.8–42.7)	24.5 (17.0–32.6)	0.331
ASA (1/2/3/4)	6/23/48/13	3/10/27/11	3/13/21/4	0.339
History of alcohol use (major/moderate/no)	21/45/27	8/23/20	13/22/7	0.038
History of smoking (yes/no)	37/56	19/32	18/24	0.583
CCI (0–1/2–4/5–9)	49/29/15	24/19/8	25/10/7	0.363
Diabetes	15/93 (18%)	11/51 (22%)	4/42 (10%)	0.116
Preoperative characteristics				
Previous radiotherapy	9/93 (10%)	5 (10%)	4 (10%)	0.939
Previous chemotherapy	3/93 (3%)	1/51 (2%)	2/42 (5%)	0.447
Previous operation in same area	14/91 (15%)	10/49 (20%)	4/42 (10%)	0.151
Perioperative data				
Tracheostomy / intubation	47 (51%)/46 (49%)	21 (41%)/30 (59%)	26 (62%)/16 (34%)	0.047
Postoperative data				
Radiation therapy postoperatively	45 (50%)	20 (43%)	25 (58%)	0.211
Chemotherapy postoperatively	20 (23%)	8 (17%)	12 (29%)	0.326

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Table 4. Surgical data of the patients (Study I–IV)*

	All (n=93)	DEX (n=51)	NON-DEX (n=42)	p
Primary lesion				
Tongue	27	13	14	
Floor of mouth	11	8	3	
Mandible	26	14	12	
Maxilla	15	9	6	
Buccal mucosa	9	5	4	
Tonsil	3	1	2	
Palate	1	1	0	
Larynx - hypofarynx	1	0	1	
Reconstruction type: Soft tissue / bone **	83/10	46/5	37/5	0.745
Flap type				0.360
Forearm flap	51	31	20	
ALT	33	15	18	
DCIA	4	2	2	
Fibula	1	1	0	
LD	1	0	1	
Scapula + LD	2	0	2	
Scapula + parascapula	1	1	0	
Neck dissection				0.207
Unilateral	78	45	33	
Bilateral	15	6	9	
Sentinel	10	7	3	
Neck dissection levels				0.201
L1-3	28	18	10	
L1 - 4/5 or radical	55	26	29	
Operation time (min)	340 (87–975)	340 (138–975)	359 (208–719)	0.373

DEX=dexamethasone group; NON-DEX=non-dexamethasone group; ALT=Anterolateral Thigh Perforator flap; LD=latissimus dorsi muscle; DCIA=The deep circumflex iliac artery bone flap; CCI=Charlson Comorbidity Index.

Alcohol use was defined as moderate if drinking was weekly or less and major if it occurred daily. Patients were defined as smokers if they smoked before surgery. Data given as median and range.

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**Free flaps including both soft-tissue and bone are classified as bone reconstructions.

Table 5. TNM classification of the patients (Study I–IV)*

	N0		N1		N2A-C		TOTAL
	DEX	NON-DEX	DEX	NON-DEX	DEX	NON-DEX	
T1–T2	22	12	2	6	3	6	51
T3–T4A-B	12	10	2	1	9	6	40
TOTAL	34	22	4	7	12	12	91
% of n	68 %	54 %	8 %	17 %	24 %	29 %	

DEX=dexamethasone group; NON-DEX=non-dexamethasone group.

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Table 6. Major complications of the patients (Study I–IV)

	ALL (n=93)	**DEX (n=51)**	**NON-DEX (n=42)**	**p**
Number of major complications (patients)	17/93 (18%)	14/51 (27%)	3/42 (7%)	0.012*
Number of major complications	20	16	4	
Venous thrombosis of the flap	6 (6%)	4 (8%)	2 (5%)	
Flap loss	3 (3%)	2 (4%)	1 (2%)	
Wound necrosis, fistula, infection	4 (4%)	4 (8%)	0	
Postoperative bleeding	1 (1%)	1 (2%)	0	
Later tracheostomy	5 (4%)	4 (8%)	1 (2%)	
Pneumothorax	1 (1%)	1 (2%)	0	
Number of minor complications (patients)	7/93 (11%)	4/51 (10%)	3/42 (12%)	0.899
Fluid collection/seroma	2 (2%)	1 (2%)	1 (2%)	
Local wound infection (neck or face)	1 (1%)	1 (2%)	0	
Hematoma/bleeding	3 (3%)	1 (2%)	2 (5%)	
Fistula	1 (1%)	1 (2%)	0	
Infection postoperatively	17/94 (18%)	10/51 (20%)	7/42 (17%)	0.715

DEX=dexamethasone group; NON-DEX=non-dexamethasone group. Data given as median and range.

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No statistical differences existed between the groups for any of the main primary outcome variables, which were neck swelling, length of ICU stay, and hospital stay, duration of intubation or tracheostomy, and delay to the start of possible radiotherapy. (**Table 7)**. Patients who received dexamethasone did not have a shorter treatment period in the ICU or ward nor was the tracheostomy or intubation time shorter.

Table 7. Primary outcome measures (Study I)

	All (n=93)	DEX (n=51)	NON-DEX (n=42)	p
Neck swelling (cm) (n=77) **	5.5 (0–13)	5.0 (0–12.5)	6.0 (1.5–13)	0.196
Length of ICU stay (days) (n=93)	3 (1–12)	3 (1–12)	3 (1–8)	0.965
Length of hospital stay (days) (n=91)	13 (5–49)	12 (5–35)	13 (6–49)	0.594
Duration of tracheostomy (days) (n=46)	8 (2–43)	6 (2–18)	9 (2–42)	0.251
Duration of intubation (days) (n=47)	1 (0–6)	1 (1–6)	1 (0–5)	0.064
Start of postoperative radiation therapy (days) (n=33)	43 (30–99)	47 (34–99)	43 (30–74)	0.110

DEX=dexamethasone group; NON-DEX=non-dexamethasone group. Data given as median and range.

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** Highest increase (cm) in neck circumference during the seven postoperative days

5.2 EFFECT OF DEXAMETHASONE ON RECOVERY FOLLOWING SURGERY OF HNC PATIENTS WITH MICROVASCULAR RECONSTRUCTION (STUDY II)

5.2.1 RECOVERY

There were no differences between the groups in parameters of postoperative mobilization, ability to drink fluids after surgery, or in other clinical measures of recovery.

5.2.2 PAIN

There was significantly less pain in the study group (p=0.030) and the total oxycodone dose over 5 days postoperatively was significantly lower as compared with the control group (p=0.040), especially during the first postoperative day **(Figure 2)**.

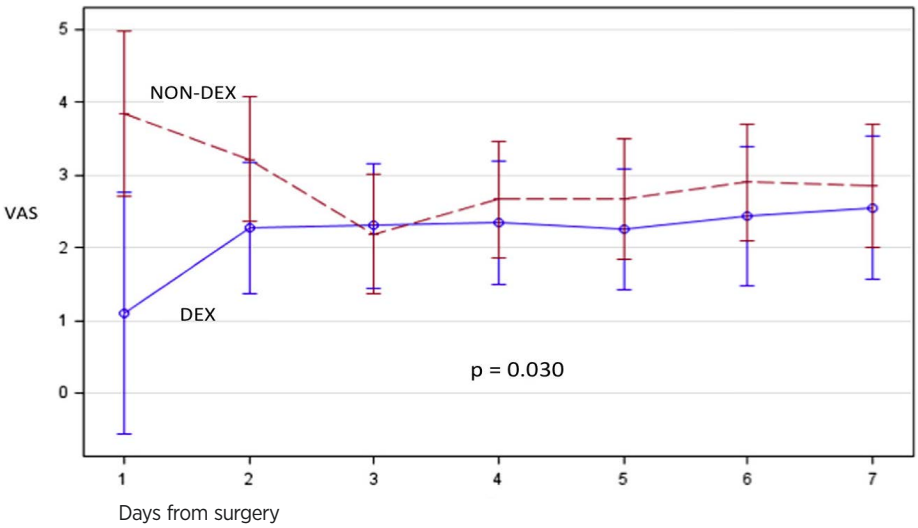

Figure 2. VAS area under the curve after FFS. Data are presented as means with 95% confidence limits. DEX=dexamethasone group; NON-DEX=control group; VAS=Visual analog scale (published in Study II).

5.2.3 PONV

Dexamethasone did not significantly reduce PONV over 5 days postoperatively ($p>0.05$). There was a statistical difference in nausea in the second postoperative day ($p=0.0264$), but the clinical difference was not significant, because the need for antiemetics was low in both groups.

5.2.4 GLUCOSE BALANCE

Patients receiving dexamethasone required significantly more insulin when compared with patients in the control group ($p<0.001$) as presented in **Figure 3**. **Table 8** summarizes the most significant outcomes of Study II.

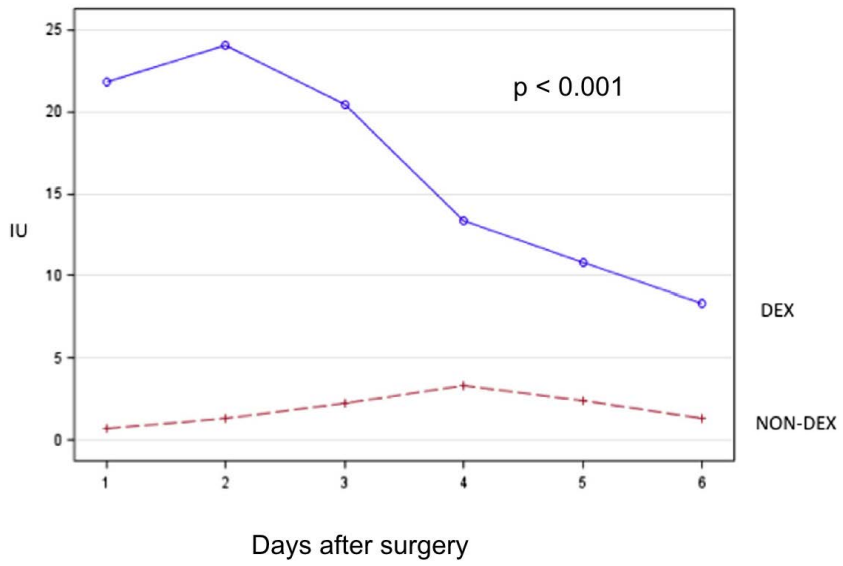

Figure 3. Insulin area under the curve after microvascular reconstruction. Data are presented as means with 95% confidence limits. DEX: dexamethasone group (blue line), NON-DEX: control group (red dashed line), IU: international units of insulin (published in Study II).

Table 8. Patients postoperative results of Study II (Modified from Study II)

	All (n=93)	DEX (n=51)	NON-DEX (n=42)	p
Length of ICU stay (days)	3 (1–12)	3 (1–12)	3 (1–8)	0.965
Length of hospital stay (days) (n=91)	13 (5–49)	12 (5–35)	13 (6–49)	0.594
Length of sedation infusion (days)	2 (0–6)	2 (1–6)	1 (0–6)	0.088
Length of opioid infusion (days)	1 (0–4)	1 (0–3)	1 (0–4)	0.497
Total dose of oxycodone in 5 days (mg)	95.2	81.2	112.1	0.040*
Total dose of ondansetron in 5 days (mg)	83 (mean 0.89)	34 (mean 0.67)	49 (mean 1.17)	0.058
Length of IV antibiotics (days)	7 (3–30)	8 (3–30)	7 (3–22)	0.209
Able to sit (days)	2 (1–6)	2 (1–6)	2 (1–6)	0.5174
Able to stand (days)	2 (1–7)	2 (1–6)	2(1–7)	0.537
Able to walk (days)	3 (1–12)	3 (1–12)	3 (1–10)	0.784
Able to drink fluids (days)	4 (1–19)	3 (1–19)	5 (1–17)	0.171

DEX=dexamethasone group; NON-DEX=non-dexamethasone group. Data given as median and range.

5.2.5 METABOLIC AND INFLAMMATORY RESPONSE

Lactate and leukocyte levels were significantly higher ($p<0.001$) during the first five postoperative days in the DEX group. CRP levels were significantly lower ($p<0.001$) and leukocyte counts were significantly higher ($p<0.001$) in patients receiving dexamethasone.

5.3 LONG-TERM QUALITY OF LIFE (STUDY III)

All patients were considered as a one group. The median time between surgery and HRQoL assessment was 4.9 years (range 3.7–7.8). Of the 93 patients, 61 (66%) were alive by the end of the follow-up (December 2016) and the number of patients who answered the long-term follow-up questionnaire was 42 (69%) (**Figure 4)**. The mean 15D score of all patients (n=42) at the 4.9-years follow-up point was significantly lower than at baseline ($p=0.010$) (**Figure 5)**. **Figure 6** shows the preoperative mean dimensions relative to the general population. The dimensions of "speech" and "usual activities" were significantly impaired at the end of the follow-up **(Figure 7)**. There was a significant difference at the 4.9-years follow-up between patients and the general population in the mean 15D score (patients 0.844 vs population 0.894, $p=0.014$). After the 4.9-years follow-up, patients were significantly ($p<0.05$) worse off in the dimensions of "speech", "eating", and "usual activities".

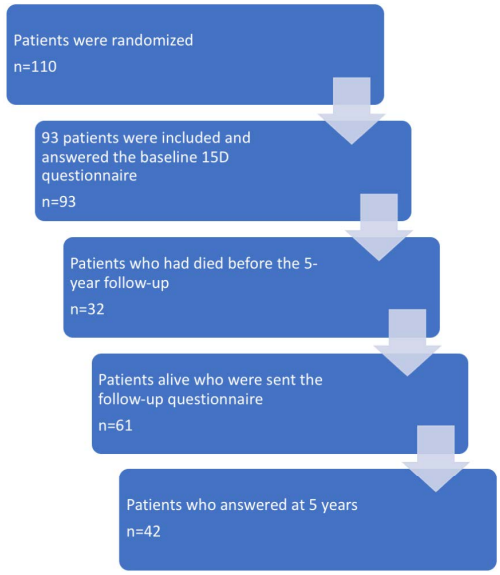

Figure 4. Flow chart of the patients (Study III)

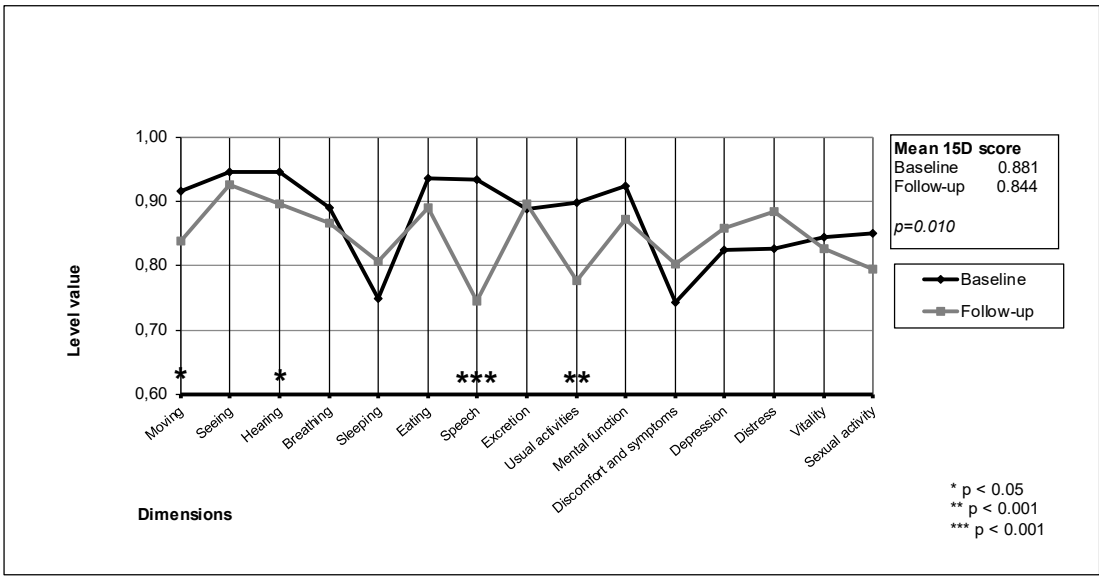

Figure 5. Mean 15D profiles of HNC patients with microvascular reconstruction (n=42) at baseline and 4.9 years after operation (Published in Study III).

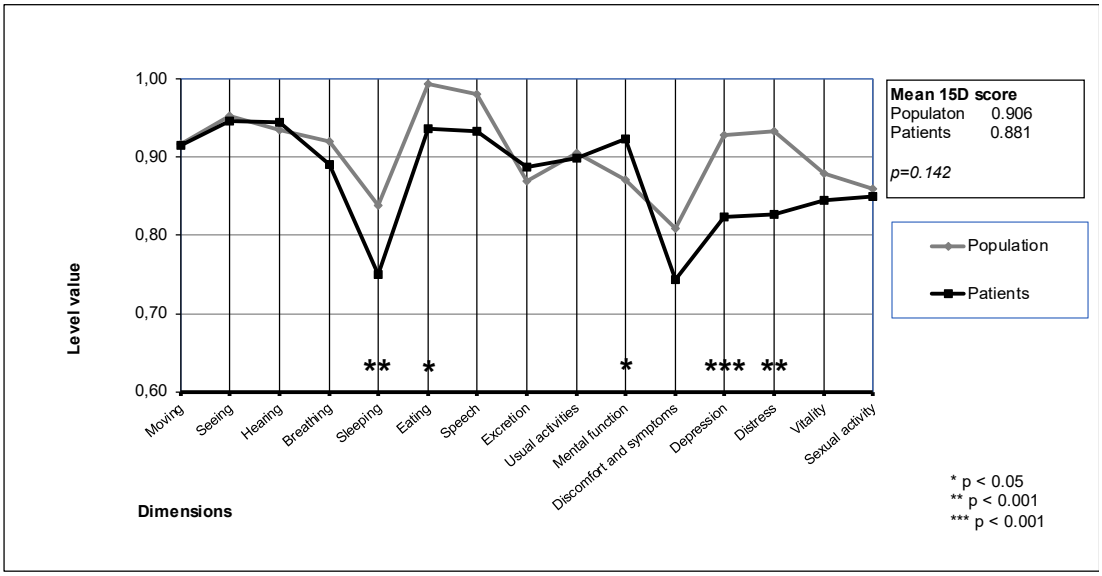

Figure 6. 15D profiles of HNC patients with microvascular reconstruction (n=42) at baseline compared with age- and gender-matched general population (Published in Study III).

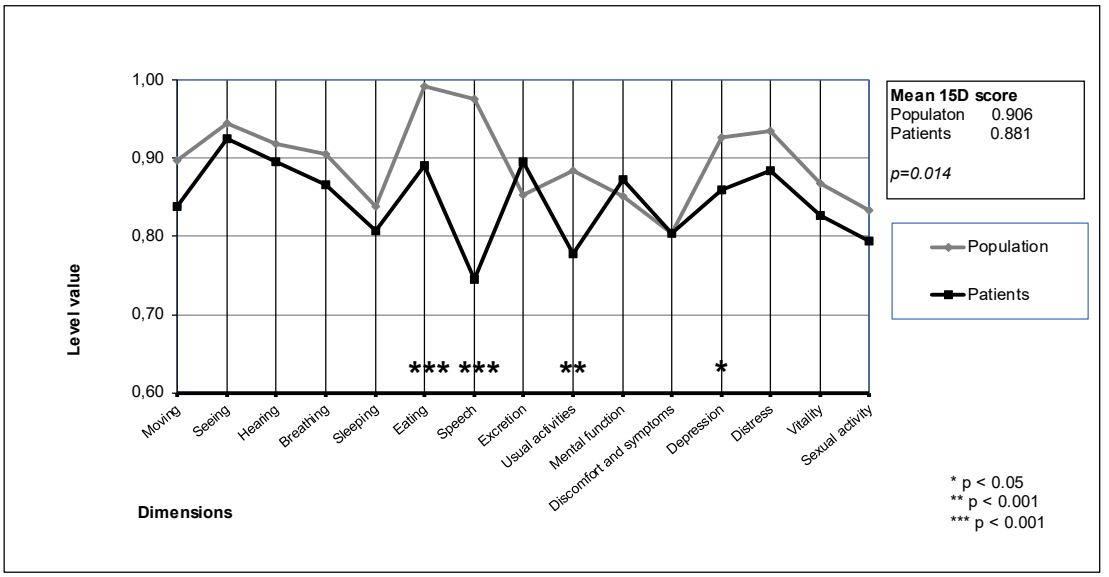

Figure 7. 15D profiles of HNC patients with microvascular reconstruction (n=42) at follow-up compared with age- and gender-matched general population (Published in Study III).

5.4 MORTALITY AND SURVIVAL (STUDY IV)

5.4.1. DEMOGRAPHIC DATA

None of the patients had radiologically diagnosed distant metastasis or locoregional recurrence preoperatively. Second primary HNC occurred in 16 patients of all (17%, diagnosis made between 32-3363 days, median 612). Locoregional metastasis on the neck occurred in 13 patients (14%, diagnosis made between 52-1982 days, median 600) and distant metastasis in 13 patients (14%, diagnosis made between 32-1982 days, median 244) during follow-up. Four patients developed other cancer than HNC during follow-up.

5.4.2 SHORT-TERM MORTALITY

There were two deceased patients within 33 days; both in the DEX group. There were significantly more deaths in the DEX group during the first six months (DEX n=7, NON-DEX n=0) and one year (DEX n=11, NON-DEX n=2, Chi-square test p=0.043) after surgery **(Figure 8)**. Five out of seven (71%) patients in the DEX

group that died during the first 6 months, experienced postoperative complications (2 numerous operations due to rapid spread of cancer, 1 pneumonia, 1 local infection, 1 venous thrombosis). The primary cause of death was HNC for all deceased patients during the first 12 postoperative months.

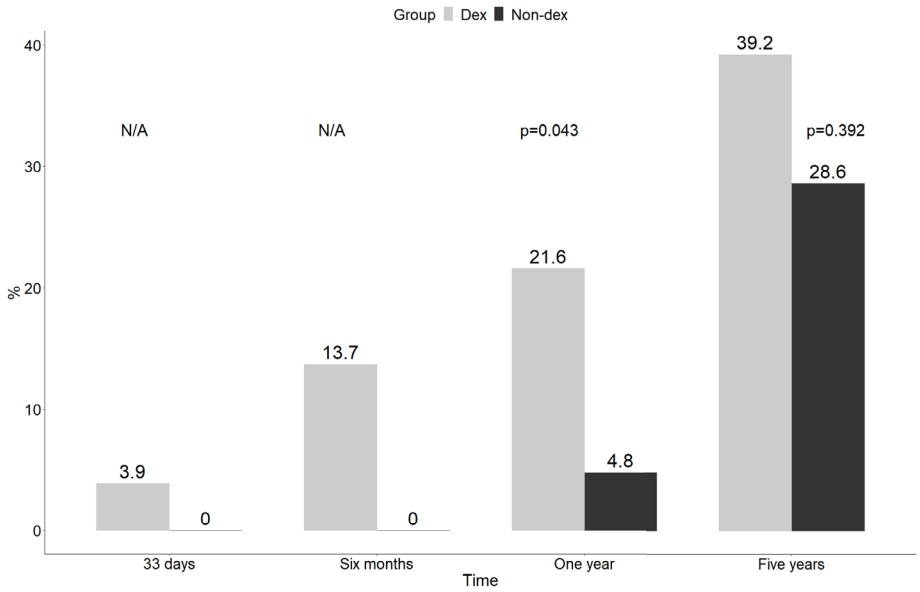

Figure 8. Number of deceased patients (n=38) between groups during the follow-up (modified from Study IV). DEX=dexamethasone group; NON-DEX=non-dexamethasone group; N/A: Statistical methods not available.

5.4.3 LONG-TERM MORTALITY

The median follow-up time was 5.3 years (range 33 days–9 years). Altogether 38 patients (41%) had died during the follow-up by the end of 2017. Locoregional metastasis occurred in 9 patients (24%, p=0.025) and distant metastasis in 12 patients (32%, p<0.001) of all the 38 deceased patients in the follow-up (p=0.025). In the long-term follow-up, deceased were more likely to have had more advanced decease (higher T classification, p=0.002; and higher stage, p=0.008), need for gastrostoma (p=0.002), received more often postoperative chemotherapy (p=0.005), and more often locoregional (p=0.025) or distal metastases (P<0.001) in the follow-up (**Table 9**). Five patients (13%) survived beyond five years but died later (latest 7.6 years after the operation).

Table 9. Comparison of study variables and survival data in follow-up (median 5.3 years) (Modified from Study IV)

	Survived (N=55)	Deceased (N=38)	Total (N=93)	p value
Group (n, %)				0.259[1]
DEX	27 (49.1)	24 (63.2)	51 (54.8)	
NON-DEX	28 (50.9)	14 (36.8)	42 (45.2)	
Gender (n, %)				0.628[1]
Female	19 (34.5)	15 (39.5)	34 (36.6)	
Male	36 (65.5)	23 (60.5)	59 (63.4)	
BMI [§]				0.284[2]
Median (Range)	24.7 (16.0–39.4)	25.6 (15.8–42.7)	24.9 (15.8–42.7)	
ASA (n, %)				0.621[1]
1	5 (9.1)	1 (2.6)	6 (6.5)	
2	14 (25.5)	9 (23.7)	23 (24.7)	
3	28 (50.9)	21 (55.3)	49 (52.7)	
4	8 (14.5)	7 (18.4)	15 (16.1)	
History of alcohol use (n, %) [§§]				0.137[1]
Major	13 (23.6)	8 (21.6)	21 (22.8)	
Moderate	30 (54.5)	14 (37.8)	44 (47.8)	
No	12 (21.8)	15 (40.5)	27 (29.3)	
History of smoking (n, %) [†]				0.704[1]
Yes	21 (38.2)	16 (42.1)	37 (39.8)	
No	34 (61.8)	22 (57.9)	56 (60.2)	
CCI (n, %)				0.082[1]
0–1	32 (58.2)	17 (44.7)	49 (52.7)	
2–4	18 (32.7)	11 (28.9)	29 (31.2)	
5–9	5 (9.1)	10 (26.3)	15 (16.1)	
Median age at operation (years, range)	64.7 (39.2–87.7)	66.0 (34.2–92.8)	65.2 (34.2–92.8)	0.522[2]
Airway access for mechanical ventilation (n, %)				0.238[1]
Intubation	30 (54.5)	16 (42.1)	46 (49.5)	
Tracheostomy	25 (45.5)	22 (57.9)	47 (50.5)	
PEG (n, %)				**0.002**[1]
Yes	19 (34.5)	23 (60.5)	42 (45.2)	
No	34 (61.8)	10 (26.3)	44 (47.3)	
Later	2 (3.6)	5 (13.2)	7 (7.5)	
Reconstruction type (n, %)				0.534[1]
Bone	5 (9.1)	5 (13.2)	10 (10.8)	
Soft tissue	50 (90.9)	33 (86.8)	83 (89.2)	
Site of the primary lesion (n, %)				0.428[1]
Maxilla	8 (14.5)	7 (18.4)	15 (16.1)	
Mandible	11 (20.0)	15 (39.5)	26 (28.0)	
Tongue	17 (30.9)	10 (26.3)	27 (29.0)	
Floor of mouth	8 (14.5)	3 (7.9)	11 (11.8)	
Buccal mucosa	7 (12.7)	2 (5.3)	9 (9.7)	
Tonsil	2 (3.6)	1 (2.6)	3 (3.2)	
Palate	1 (1.8)	0 (0.0)	1 (1.1)	
Larynx - hypopharynx	1 (1.8)	0 (0.0)	1 (1.1)	
Flap type (n, %)				0.053[1]
ALT	17 (30.9)	15 (39.5)	32 (34.4)	
Forearm flap	35 (63.6)	16 (42.1)	51 (54.8)	
Other [††]	3 (5.5)	7 (18.4)	10 (10.8)	

Neck dissection (n, %)				0.283[1]
Unilateral	48 (87.3)	30 (78.9)	78 (83.9)	
Bilateral	7 (12.7)	8 (21.1)	15 (16.1)	
Neck dissection levels (n, %)				0.506[1]
Sentinel node biopsy	6 (10.9)	4 (10.5)	10 (10.8)	
1–3	19 (34.5)	9 (23.7)	28 (30.1)	
1–4/5 or radical	30 (54.5)	25 (65.8)	55 (59.1)	
pT‡ (Mean (SD))	2.07 (1.36)	2.97 (1.21)	2.44 (1.37)	**0.002**[3]
Stage (n, %) ‡‡				**0.008**[1]
1	24 (43.6)	4 (10.8)	28 (30.4)	
2	4 (7.3)	3 (8.1)	7 (7.6)	
3	5 (9.1)	4 (10.8)	9 (9.8)	
4	22 (40.0)	26 (70.3)	48 (52.2)	
Radiation therapy postoperatively (n, %)				0.076[1]
No	32 (58.2)	15 (39.5)	47 (50.5)	
Yes	23 (41.8)	23 (60.5)	46 (49.5)	
Chemotherapy postoperatively (n, %) #				**0.005**[1]
No	47 (85.5)	22 (59.5)	69 (75.0)	
Yes	8 (14.5)	15 (40.5)	23 (25.0)	
Major complication (n, %)				0.096[1]
No	48 (87.3)	28 (73.7)	76 (81.7)	
Yes	7 (12.7)	10 (26.3)	17 (18.3)	
Second primary in follow-up (n, %)				0.414[1]
No	47 (85.5)	30 (78.9)	77 (82.8)	
Yes	8 (14.5)	8 (21.1)	16 (17.2)	
Distant metastasis in follow-up (n, %)				**<0.001**[1]
No	54 (98.2)	26 (68.4)	80 (86.0)	
Yes	1 (1.8)	12 (31.6)	13 (14.0)	
Locoregional metastasis in follow-up (n, %)				**0.025**[1]
No	51 (92.7)	29 (76.3)	80 (86.0)	
Yes	4 (7.3)	9 (23.7)	13 (14.0)	

DEX: Dexamethasone group

NON-DEX: Non-dexamethasone group

N: Number

BMI: Body Mass Index

ASA: American Society of Anesthesiologists

CCI: Charlson Comorbidity Index

PEG: Percutaneous endoscopic gastrotomy

§ Data are missing from one patient

§§ Alcohol use was defined as moderate if drinking was weekly or less and major if it occurred daily, data are missing from two patients

† Patients were defined as smokers if they smoked before surgery

ALT: Anterolateral Thigh Perforator flap

†† Other: 4 DCIA (the deep circumflex iliac artery bone flap), 1 fibular flap, 1 LD (Latissimus dorsi muscle flap), 2 Scapular + LD flap and 1 Scapular + parascapular flap

‡ pT=Pathological tumor classification, data are missing from two patients

‡‡ Data are missing from two patients

Data are missing from two patients

$p < 0.05$ (significant)

[1]: Pearson's Chi-squared test

[2]: Kruskal-Wallis rank sum test

[3]: Linear Model ANOVA (Mann-Whitney with two groups)

Altogether 32 patients had died within five years, therefore the 5-year OS for all patients (n=93) was 65.6%. OS for all patients for the whole follow-up period (median 5.3 years) was 59% (55/93). Even though there were more deaths in DEX groups during the whole follow-up period, according to the Kaplan-Meier curve and log-rank test, there was no statistically significant difference in long-term survival between the treatment groups **(Figure 9)**.

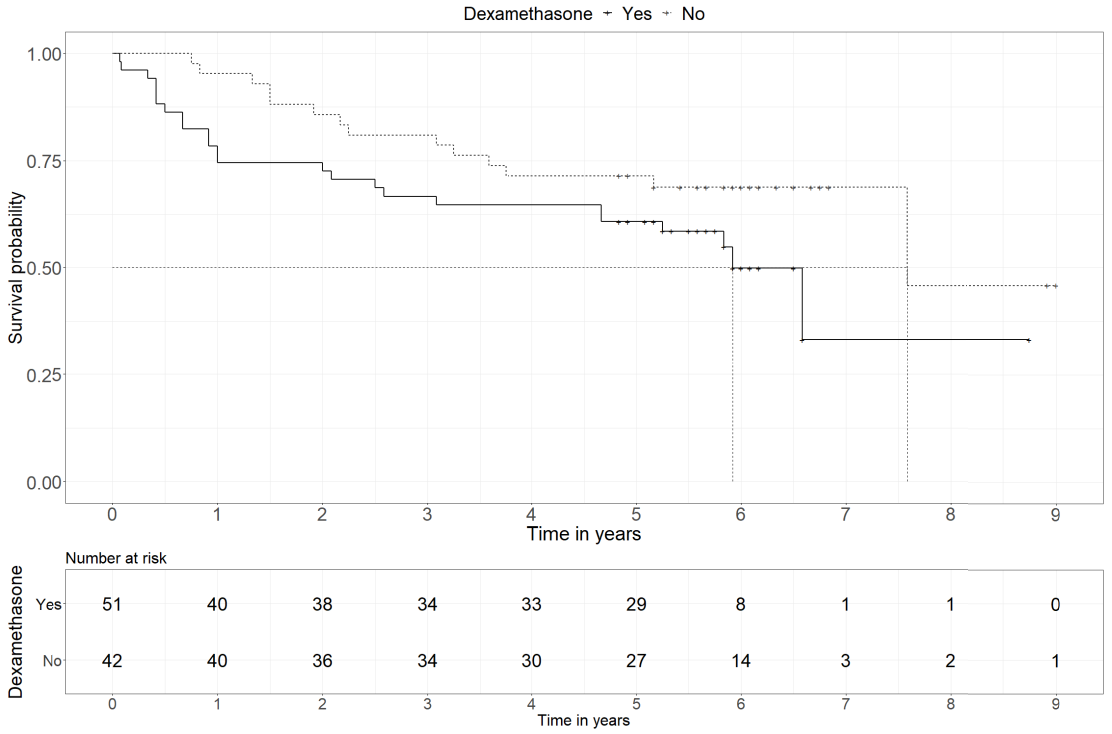

Figure 9. Survival curves. There was 24 events (hazard=0.115) in DEX group, and 14 events (hazard=0.0673) in NON-DEX group. Log-rank statistic was 0.094 for the whole follow-up, and 0.019 after 12 months.

For an initial multivariate Cox model, we identified 13 confounders. After adjustment, contrary to the univariate analysis, the use of dexamethasone predicted excess risk of mortality (p=0.004). Also, the reduced model suggests, that the other statistically significant long-term predictors of death and poor OS during follow-up were CCI 5–9 and presence of distant metastasis **(Table 10)**.

Table 10. Factors affecting long-term mortality in follow-up (5.3 years) (modified from Study IV)

OVERALL SURVIVAL		ALL	HR (multivariable)	HR (multivariable reduced)
Group	DEX	51	-	-
	NON-DEX	42	0.22 (0.09–0.56, p=0.001)	0.31 (0.14–0.69, **p=0.004**)
pT §	1	38	-	-
	2	15	3.07 (0.77–12.26, p=0.111)	2.58 (0.74–9.03, p=0.137)
	3	3	5.16 (0.83–32.00, p=0.078)	3.13 (0.56–17.59, p=0.196)
	4	37	4.22 (1.47–12.09, p=0.007)	2.56 (0.98–6.71, p=0.055)
PEG	Yes	42	-	-
	No	44	0.22 (0.06–0.74, p=0.015)	0.37 (0.14–1.04, p=0.059)
	Later	7	2.74 (0.61–12.34, p=0.188)	2.09 (0.58–7.51, p=0.256)
Major complication (n)	No	76	-	-
	Yes	17	0.94 (0.30–2.90, p=0.910)	1.59 (0.65–3.89, p=0.312)
CCI	0–1	49	-	-
	2–4	29	3.79 (1.14–12.59, p=0.029)	1.57 (0.64–3.83, p=0.322)
	5–9	15	7.29 (2.33–22.83, p=0.001)	5.82 (2.26–14.98, **p<0.001**)
History of alcohol use (n) §§	Major	22	-	-
	Moderate	44	0.81 (0.26–2.51, p=0.721)	0.84 (0.32–2.18, p=0.722)
	No	27	2.35 (0.74–7.45, p=0.146)	1.53 (0.54–4.34, p=0.421)
Radiation therapy postoperatively (n)	No	47	-	-
	Yes	46	0.83 (0.27–2.59, p=0.752)	-
Age at operation	Mean (SD)	65.3 (11.0)	1.00 (0.96–1.05, p=0.848)	-
Gender (n)	Female	34	-	-
	Male	59	0.72 (0.28–1.80, p=0.478)	-
BMI	Mean (SD)	25.6 (4.9)	1.05 (0.96–1.14, p=0.277)	-
Second primary in follow-up (n)	No	77	-	-
	Yes	16	0.51 (0.14–1.77, p=0.286)	-
Distant metastasis in follow-up (n)	No	80	-	-
	Yes	13	16.10 (5.13–50.52, p<0.001)	10.41 (3.99–27.13, **p<0.001**)
Locoregional metastasis in follow-up (n)	No	80	-	-
	Yes	13	2.82 (1.00–7.94, p=0.050)	-
Chemotherapy postoperatively (n) #	No	69	-	-
	Yes	23	1.83 (0.51–6.54, p=0.352)	-

DEX: Dexamethasone group
NON-DEX: Non-dexamethasone group
N = number
§ pT=Pathological tumor classification, data are missing from one patient
CCI: Charlson Comorbidity Index
§§ Alcohol use was defined as moderate if drinking was weekly or less and major if it occurred daily, data are missing from two patients
BMI: Body Mass Index
Data are missing from two patients

5.4.4 CAUSES OF DEATH

The primary cause of death was HNC for most of the deceased patients (30/38, 79%). The primary cause of death was HNC in all patients who died during the first 6 months (n=7, 18,4%) as well as during the 6–12 months (n=13, 34.2%). Three patients died because of another cancer (one prostate cancer, one colon cancer, and one bladder cancer). Five patients died for other causes (four cardiovascular disease, one alcoholic liver cirrhosis). Causes of death and time for all the patients can be seen in **Table 11.**

Table 11. Causes of death for 38 deceased patients

	ALL (n = 93)	DEX (n = 51)	NON-DEX (n = 42)	P	Primary cause of death, n
Number, n (%)					
< 33 days	2 (2)	2 (4)	0		
< 6 months	7 (18)	7 (16)	0		HNC (7)
< 12 months	13 (34)	11 (28)	2 (6)	0.043*	HNC (13)
5 years	31 (61)	20 (39)	12 (29)	0.259	
During follow-up	38 (41)	24 (47)	14 (33)	0.180	
Primary cause of death					
HNC	28 (74)	19 (80)	11 (79)	0.415	
Non-HNC	3 (8)	1 (4)	2 (14)		
Other cause of death**	5 (13)	4 (17)	1 (7)		

DEX=dexamethasone group; NON-DEX=non-dexamethasone group; HNC=Head and neck cancer.
*p<0.05 (significant)
**1 Liver cirrhosis, 4 cardiovascular disease

6. DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

This is the first prospective, double-blind randomized controlled trial to study whether perioperative use of dexamethasone in reconstructive HNC surgery is beneficial for the patients. As in many other fields of surgery, in reconstructive surgery perioperative GCs are widely used to treat patients because they are believed to reduce pain, PONV, and the risk of immediate complications, like prolonged intubation and sedation; they are also considered to prevent edema in the area of anastomosis, which can lead to possible flap loss, and thus improve recovery. Patients benefit by experiencing recovery without complications. Prolonged periods of treatment often cause postoperative problems like delay of possible adjuvant oncological treatments. This thesis reports the significant findings of the perioperative use of GCs, long-term HRQoL, and mortality of HNC patients with microvascular reconstruction.

6.2 USE OF GLUCOCORTICOIDS IN ASSOCIATION WITH RECONSTRUCTIVE HNC SURGERY

6.2.1 COMPLICATIONS AND INFLUENCE OF DEXAMETHASONE

The findings of the present study revealed that major complications occurred significantly more frequently in patients administered GCs than in the control group (153, 154). In addition, all infections that needed surgical interventions occurred only in patients receiving dexamethasone, and none in the control group. There is previous evidence of contradictory results regarding the influence of perioperative GCs on postoperative complications and infections (123, 155). In the study of Percival et al., the authors concluded that intraoperative administration of dexamethasone for anti-emetic purposes may confer an increased risk of postoperative infection (121). The operations in the analysis included orthopedic, thoracic, neurosurgical, ENT, vascular, urology, plastic, breast, colonic, and gastroenterological procedures but the amounts of dexamethasone were relatively small. The study of Mastropietro et al. (121) was the first to publish an association between infection and increased cumulative duration of GC after pediatric cardiac surgery. The authors reviewed the files of 76 children, all of whom had received postoperative hydrocortisone. Altogether 86% of the children received perioperative dexamethasone and 36% of

the children had postoperative infections that were significantly associated with GC exposure (122). There are no previously published publications of the association with GC use and reconstructive HNC surgery.

6.2.2 RECOVERY

The current study demonstrated that the use of dexamethasone had little effect on immediate postoperative recovery. Before this study, all reconstructive HNC patients received perioperative dexamethasone in Helsinki University Hospital, Finland and it was expected that it would decrease edema in the neck area, which would hasten recovery. In this study, the use of dexamethasone did not shorten the operation time nor the duration of tracheostomy, intubation, or sedation. Similarly, dexamethasone did not shorten either the length of ICU or hospital stay, nor hasten the ability to sit, stand, walk, and drink fluids. There was no effect on the delay of starting adjuvant radiotherapy within the patient groups. Furthermore, the use of dexamethasone did not accelerate the recovery process. This is in line with Jean et al. who made a systematic review and meta-analysis of the effects of perioperative systemic GCs in patients undergoing orthognathic surgery and found no beneficial evidence for the length of the hospital stay (156).

6.2.3 PAIN

There are many publications in different fields of surgery that describe the perioperative use of GCs to reduce pain (104, 106, 107). This was the only benefit of the use of GCs with HNC patients in the current study. Although patients in the DEX group reported significantly less pain and needed less oxycodone during the five postoperative days, the routine use of dexamethasone is not justified in this patient group, because it causes other disadvantages. This finding is in line with Afman et al., who made a meta-analysis of eight randomized trials testing the use of dexamethasone to reduce post-tonsillectomy pain for pediatric patients and concluded that dexamethasone may reduce pain, but consideration of routine use seems reasonable because of the adverse side-effects (157). Clayburgh et al. showed in their randomized, controlled study of HNC patients undergoing transoral robotic surgery, that extended perioperative GC use may decrease the length of hospital stay, although there was no significant difference in pain measured between the groups (158).

6.2.4 PONV

Dexamethasone is often used by anesthesiologists to reduce the risk of PONV in surgical patients. In the current study, perioperative dexamethasone failed to significantly reduce PONV in five days postoperatively. A similar phenomenon was observed in studies by Jahromi et al., and also Furst et al. (159, 160). Wattwil et al. studied PONV following breast surgery and assessed that ondansetron or dexamethasone are equally effective in the prevention of PONV (161). Haapanen et al. investigated the effect of dexamethasone on PONV in 119 facial fracture patients in their prospective, randomized study and concluded that the difference of PONV between the groups was only minor thus alternative medications should be used for prevention of PONV in this patient group (162).

6.2.5 GLUCOSE BALANCE AND METABOLIC / INFLAMMATORY RESPONSE

Patients required significantly more insulin in the DEX group in the current study. Dieleman et al. showed in their multicenter, randomized, double-blind, placebo-controlled trial of 4494 patients undergoing cardiac surgery with cardiopulmonary bypass that dexamethasone was associated with higher postoperative glucose levels and the use of dexamethasone did not benefit the patients (163). Surgery causes changes in blood count. Ottens et al. showed in their randomized controlled trial of 498 patients that the administration of intraoperative high-dose dexamethasone was associated with significantly higher postoperative lactate and glucose levels after cardiac surgery (164). It is well known that GCs reduce the systemic inflammatory response caused by surgical trauma. Use of GCs is associated with postoperative leukocytosis and lower CRP levels (165-167). Postoperative leukocyte and CRP concentrations have been found to be useful markers of the magnitude of the operative injury (168, 169). Also, in the current material, CRP levels were significantly lower, and leukocyte count significantly higher as was expected in patients receiving dexamethasone. Low CRP values, in particular, might cause doctors not to notice early-onset infections.

6.3 LONG-TERM HEALTH RELATED QUALITY OF LIFE WITH HNC PATIENTS AND MICROVASCULAR RECONSTRUCTION

There are surprisingly few studies published regarding long-term HRQoL after microvascular reconstruction surgery of HNC patients. Pierre et al. showed in their prospective study of 64 patients that long-term QoL after oncologic surgery and microvascular free flap reconstruction in patients with oral cancer is satisfactory

(129). Bozec et al. studied long-term QoL and psychosocial outcomes after oropharyngeal cancer surgery and radial forearm free-flap reconstruction and observed that long-term QoL was well-preserved (170). In the current study, the mean 15D score at the 4.9-years follow-up point was significantly lower than at baseline.

Speech problems are expected to be common after surgery of oropharyngeal cancer. The dimensions of "speech" and "usual activities" were the most affected dimensions at the 4.9-years follow-up also in the current study. Psychological distress (swallowing and speech problems, changed appearance, fear of recurrence and death) is common, even long after treatment in HNC patients (171). In the present study, the dimension of "discomfort and symptoms", and the psychological dimensions of "depression" and "distress" interestingly improved during the long-term follow-up although the differences were not statistically significant. If any anxiety occurs during the treatment period or follow-up visits, patients will have access to psychotherapy in our hospital. This may improve the depression, as well as the continuity of treatment and regular controls are beneficial for mental health.

In this study population, the mean 15D score deteriorated in all patients in the same way, regardless of whether or not postoperative radiotherapy was received. The type of reconstruction and tumor score had no statistically significant effect on the follow-up 4.9-years mean 15D score.

6.4 MORTALITY

6.4.1 SHORT-TERM MORTALITY AND INFLUENCE OF DEXAMETHASONE

There are different determinations for short-term mortality, including within 30-180 days after operation or diagnosis (172, 173). In the current study, short-term mortality was defined as death within one year after primary surgery and long-term mortality as death later than one year after the operation. The hypothesis was that perioperatively administered dexamethasone may be harmful for the patients as it can increase postoperative complications and thus cause more serious side effects. It was anticipated that perioperative dexamethasone might have effects on patients' short-term survival as it induces generalized immunosuppression and thus may cause more infectious complications. In addition, dexamethasone can significantly suppress cell proliferation and promote resistance to apoptosis in tumor cells (174, 175). The novel finding of Study IV is in line with the hypothesis, as all patients who died within six months and most who died within one year of the operation, were in the DEX group. Almost all of them had postoperative complications. This

is understood to be the first prospective randomized study to investigate the effect of the use of GCs on mortality with operated reconstructive HNC patients.

6.4.2 LONG-TERM MORTALITY

Half of the deaths occurred within two years after the surgery. The 5-year survival of the current study was 65.6%, which can be considered good, and it was higher than reported in many other series of HNC patients with free flap reconstruction (147, 176, 177). In the multivariate analysis, the most significant long-term predictors of death were distant metastases, CCI 5-9 and DEX group, whereas gender and age were not associated with long-term survival. Deceased patients were more likely to have had more advanced decease, need for gastrostoma, received more often postoperative chemotherapy, and more often locoregional or distal metastases in the follow-up. In these cases, postoperative chemotherapy is combined with radiotherapy and given in metastatic diseases, therefore the prognosis of these patients is worse originally. In the material of the current study, early death of patients also had a long-term effect, as the differences between the groups did not even out during the follow-up. The use of perioperative dexamethasone in HNC patients has been discontinued in the host institute because of the findings of the current studies.

6.4.3 CAUSES OF DEATH

There are few earlier studies that have reported causes of the death of HNC patients with microvascular reconstruction. The present study reported the primary disease (HNC) as the main cause of death in most (79%) of the patients, which is in line with findings by Ch'ng et al. and Lahtinen et al. (13, 178). Some studies have reported the second primary malignancy to be the leading cause of death among HNC patients, but these include all HNC patients, not only those with microvascular reconstruction (149, 179). In the current study, other malignancies were not predominating.

6.5 LIMITATIONS OF THE THESIS AND FUTURE PROSPECTS

The relatively small size of the study population can be considered as a limitation of this thesis. However, patients in this study participated in a blinded prospective randomized dexamethasone study and formed a coherent and representative group of patients with a relatively rare type of cancer and microvascular reconstruction.

Surgical procedure is very specific, and it took a long time to collect this material. Accordingly, the number of the patients may be considered quite sufficient, and this is a thoroughly conducted study in which the goal has been well defined. The impact of surgical margins on deaths was not analyzed in the cohort, however, which is a limitation.

Perioperative dexamethasone is still used for this patient group in many centers. The findings of these articles are novel for HNC patients and the information of this thesis needs to be shared to the centers who are still using it. The effects of perioperative dexamethasone need to be studied in the future also with other types of cancer surgeries.

7. CONCLUSIONS

At the beginning of this prospective study, it was hypothesized that reconstructive HNC patients receiving dexamethasone would recover faster. Contrary to early expectations, the results of this study showed that perioperative use of dexamethasone was harmful for this patient group and is not recommended for HNC patients requiring microvascular reconstruction. It is associated with major complications and short-term morbidity and it does not seem to significantly enhance immediate postoperative recovery or shorten ICU or hospital stay. There is more harm than benefit in the perioperative use of dexamethasone with reconstructive HNC patients. This study revealed the following key findings.

I
Perioperative use of dexamethasone did not benefit the HNC patients with microvascular reconstruction. Patients who received dexamethasone had significantly more major complications (need for second surgery within three weeks), especially surgical infections. Use of dexamethasone did not diminish the amount of neck swelling, length of ICU or hospital stay, or duration of intubation or tracheostomy.

II
Perioperative use of dexamethasone did not enhance recovery. Although dexamethasone decreased postoperative pain, it did not decrease nausea. There were no differences between the groups in postoperative mobilization, ability to drink fluids after surgery, or in other clinical measures of recovery. Patients required significantly more insulin and lactate levels were higher compared with controls.

III
The long-term (4.9-years) HRQoL of operated HNC patients was significantly reduced than at baseline. The most affected dimensions were “speech” and “usual activities”. There was a significant difference at the 4.9-years follow-up in the mean 15D score between patients and the general population (patients 0.844 vs population 0.894, p=0.014).

IV
Perioperative use of dexamethasone increased short-term mortality in HNC patients with microvascular reconstruction within one year after surgery. In the multivariate analysis, the most important long-term (median 5.3 years) predictors of death were distant metastases, CCI 5-9 and DEX group. The most common cause of death after microvascular surgery for HNC was the primary disease (79% of all deceased).

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Helsinki, April 2020

Satu Kainulainen

APPENDIX

QUALITY OF LIFE QUESTIONNAIRE (15D©)

Please read through all the alternative responses to each question before placing a cross (x) against the alternative which best describes **your present health status**. Continue through all 15 questions in this manner, giving only **one** answer to each.

QUESTION 1. MOBILITY
1 ( ) I am able to walk normally (without difficulty) indoors, outdoors and on stairs.
2 ( ) I am able to walk without difficulty indoors, but outdoors and/or on stairs I have slight difficulties.
3 ( ) I am able to walk without help indoors (with or without an appliance), but outdoors and/or on stairs only with considerable difficulty or with help from others.
4 ( ) I am able to walk indoors only with help from others.
5 ( ) I am completely bed-ridden and unable to move about.

QUESTION 2. VISION
1 ( ) I see normally, i.e. I can read newspapers and TV text without difficulty (with or without glasses).
2 ( ) I can read papers and/or TV text with slight difficulty (with or without glasses).
3 ( ) I can read papers and/or TV text with considerable difficulty (with or without glasses).
4 ( ) I cannot read papers or TV text either with glasses or without, but I can see enough to walk about without guidance.
5 ( ) I cannot see enough to walk about without a guide, i.e. I am almost or completely blind.

QUESTION 3. HEARING
1 ( ) I can hear normally, i.e. normal speech (with or without a hearing aid).
2 ( ) I hear normal speech with a little difficulty.
3 ( ) I hear normal speech with considerable difficulty; in conversation I need voices to be louder than normal.
4 ( ) I hear even loud voices poorly; I am almost deaf.
5 ( ) I am completely deaf.

QUESTION 4. BREATHING
1 ( ) I am able to breathe normally, i.e. with no shortness of breath or other breathing difficulty.
2 ( ) I have shortness of breath during heavy work or sports, or when walking briskly on flat ground or slightly uphill.
3 ( ) I have shortness of breath when walking on flat ground at the same speed as others my age.
4 ( ) I get shortness of breath even after light activity, e.g. washing or dressing myself.
5 ( ) I have breathing difficulties almost all the time, even when resting.

QUESTION 5. SLEEPING

1 ( ) I am able to sleep normally, i.e. I have no problems with sleeping.
2 ( ) I have slight problems with sleeping, e.g. difficulty in falling asleep, or sometimes waking at night.
3 ( ) I have moderate problems with sleeping, e.g. disturbed sleep, or feeling I have not slept enough.
4 ( ) I have great problems with sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning.
5 ( ) I suffer severe sleeplessness, e.g. sleep is almost impossible even with full use of sleeping pills, or staying awake most of the night.

QUESTION 6. EATING

1 ( ) I am able to eat normally, i.e. with no help from others.
2 ( ) I am able to eat by myself with minor difficulty (e.g. slowly, clumsily, shakily, or with special appliances).
3 ( ) I need some help from another person in eating.
4 ( ) I am unable to eat by myself at all, so I must be fed by another person.
5 ( ) I am unable to eat at all, so I am fed either by tube or intravenously.

QUESTION 7. SPEECH

1 ( ) I am able to speak normally, i.e. clearly, audibly and fluently.
2 ( ) I have slight speech difficulties, e.g. occasional fumbling for words, mumbling, or changes of pitch.
3 ( ) I can make myself understood, but my speech is e.g. disjointed, faltering, stuttering or stammering.
4 ( ) Most people have great difficulty understanding my speech.
5 ( ) I can only make myself understood by gestures.

QUESTION 8. EXCRETION

1 ( ) My bladder and bowel work normally and without problems.
2 ( ) I have slight problems with my bladder and/or bowel function, e.g. difficulties with urination, or loose or hard bowels.
3 ( ) I have marked problems with my bladder and/or bowel function, e.g. occasional 'accidents', or severe constipation or diarrhea.
4 ( ) I have serious problems with my bladder and/or bowel function, e.g. routine 'accidents', or need of catheterization or enemas.
5 ( ) I have no control over my bladder and/or bowel function.

QUESTION 9. USUAL ACTIVITIES

1 ( ) I am able to perform my usual activities (e.g. employment, studying, housework, free-time activities) without difficulty.
2 ( ) I am able to perform my usual activities slightly less effectively or with minor difficulty.
3 ( ) I am able to perform my usual activities much less effectively, with considerable difficulty, or not completely.
4 ( ) I can only manage a small proportion of my previously usual activities.
5 ( ) I am unable to manage any of my previously usual activities.

QUESTION 10. MENTAL FUNCTION

1 ( ) I am able to think clearly and logically, and my memory functions well
2 ( ) I have slight difficulties in thinking clearly and logically, or my memory sometimes fails me.
3 ( ) I have marked difficulties in thinking clearly and logically, or my memory is somewhat impaired.
4 ( ) I have great difficulties in thinking clearly and logically, or my memory is seriously impaired.
5 ( ) I am permanently confused and disoriented in place and time.

QUESTION 11. DISCOMFORT AND SYMPTOMS

1 ( ) I have no physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
2 ( ) I have mild physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
3 ( ) I have marked physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
4 ( ) I have severe physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
5 ( ) I have unbearable physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.

QUESTION 12. DEPRESSION

1 ( ) I do not feel at all sad, melancholic or depressed.
2 ( ) I feel slightly sad, melancholic or depressed.
3 ( ) I feel moderately sad, melancholic or depressed.
4 ( ) I feel very sad, melancholic or depressed.
5 ( ) I feel extremely sad, melancholic or depressed.

QUESTION 13. DISTRESS

1 ( ) I do not feel at all anxious, stressed or nervous.
2 ( ) I feel slightly anxious, stressed or nervous.
3 ( ) I feel moderately anxious, stressed or nervous.
4 ( ) I feel very anxious, stressed or nervous.
5 ( ) I feel extremely anxious, stressed or nervous.

QUESTION 14. VITALITY

1 ( ) I feel healthy and energetic.
2 ( ) I feel slightly weary, tired or feeble.
3 ( ) I feel moderately weary, tired or feeble.
4 ( ) I feel very weary, tired or feeble, almost exhausted.
5 ( ) I feel extremely weary, tired or feeble, totally exhausted.

QUESTION 15. SEXUAL ACTIVITY

1 ( ) My state of health has no adverse effect on my sexual activity.
2 ( ) My state of health has a slight effect on my sexual activity.
3 ( ) My state of health has a considerable effect on my sexual activity.
4 ( ) My state of health makes sexual activity almost impossible.
5 ( ) My state of health makes sexual activity impossible.

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